IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Serial No. : 09/853,298

Applicants : Nancy P. CAMACHO et al.

Filed : May 10, 2001

For : DETERMINATION OF THE ULTRASTRUCTURE OF CONNECTIVE TISSUE BY AN...

Art Unit : 3737

Examiner : Ruth S. Smith

Docket No. : 00328/RSB

Customer No.: 01933

Confirmation No.: 6040

DECLARATION UNDER 37 CFR 1.132 OF DR. NANCY P. CAMACHO

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTENTION: MAIL STOP AMENDMENT

S I R :

I, Dr. Nancy P. Camacho, declare as follows:

1. I am a coinventor of the above-identified application.

2. A copy of my curriculum vitae is attached hereto.

3. A telephone interview was held with the Examiner on September 22, 2004. On September 21, 2004, a PowerPoint presentation that I prepared was e-mailed to the Examiner by the patent attorney handling this matter. During the September 22, 2004 telephone interview with the Examiner, I discussed the

aforesaid PowerPoint presentation with the Examiner. Copies of slides of the aforesaid PowerPoint presentation are submitted concomitantly herewith. The last three enclosed slides were not attached to the aforesaid e-mail to the Examiner, but were discussed with the Examiner during the telephone interview.

4. Attached hereto is a discussion of the enclosed PowerPoint slides.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 10/5/04 By: Nancy P Camacho
Dr. Nancy P. Camacho

CURRICULUM VITAE

NAME: Nancy Pleshko Camacho, PhD

OFFICE ADDRESS: Research Division, Hospital for Special Surgery , 535 E. 70th St., New York, NY 10021

HOME ADDRESS: 76 Calvert Ave W, Edison, NJ 08820

HOME PHONE: 732-452-0155

CELL PHONE: 732-754-8413

EMAIL: camachon@hss.edu

CITIZENSHIP: USA

DATE AND PLACE OF BIRTH: 6-22-63
Bronxville, New York

MARITAL STATUS:

EDUCATIONAL BACKGROUND

1992-94	Postdoctoral Fellow, Departments of Biomechanics and Ultrastructural Biochemistry, The Hospital For Special Surgery, New York, NY Advisors: Adele Boskey, Ph.D. and Clare Rimnac, Ph.D.
1991-92	Postdoctoral Research Associate, Protein Crystallography, Depart. of Chemistry, Rutgers University, New Brunswick, NJ Advisor: Helen Berman, Ph.D.
1988- 1991	Rutgers University, Dept. of Chemistry, Newark, NJ Ph.D. Chemistry 1991 Thesis: "Applications of Fourier Transform Infrared Microscopy to Biomineralization ". Thesis advisors: Richard Mendelsohn, Ph.D. and Adele Boskey, Ph.D.
1986- 1988	Rutgers University, Dept. of Chemistry, Newark, NJ M.S. Medicinal Chemistry, 1988
1981 - 1985	McGill University, Montreal, Quebec, Canada B.S. Chemistry 1985

PROFESSIONAL POSITIONS AND EMPLOYMENT

1999-Current Associate Scientist. Research Division, Hospital for Special Surgery, New York, NY
Research Interests: Ultrastructure and mechanical behavior of bone and cartilage: Spectroscopic imaging of connective tissues; Cartilage repair; Mineralization abnormalities in bone disease: Pathologic calcification: Fracture healing.

1994 - 1999 Assistant Scientist. Research Division, Hospital for Special Surgery, New York, NY
1993-94 Adjunct Instructor. Department of Chemistry, Rutgers University, Newark, NJ

UNIVERSITY /MEDICAL COLLEGE AFFILIATIONS

1/2004- Current Associate Professor, Program in Physiology, Biophysics, and Systems Biology, Weill Graduate School of Medical Sciences, Cornell University, New York, NY
2002-Current Associate Professor of Biomedical Engineering , Department of Mechanical Engineering, The City University of New York, New York, NY
1999-2002 Visiting Associate Professor of Biomedical Engineering , Department of Mechanical Engineering, The City University of New York, New York, NY
1994-98 Visiting Assistant Professor of Biomedical Engineering , Department of Mechanical Engineering, The City University of New York, New York, NY

PROFESSIONAL MEMBERSHIPS

American Society for Bone and Mineral Research
Orthopaedic Research Society
Osteoarthritis Research Society International
American Society for Matrix Biology

HONORS AND AWARDS

2002; Whitehead Fellow in Musculoskeletal Research, Hospital for Special Surgery, New York, NY
2000; Women in Science Recognition. Avenue Magazine
1998; Young Investigator Award, 6th Intl Conference, Chem. & Biol. of Mineralized Tissues
1996; Eastern Orthopaedic Association Founder's Award
1995; Young Investigator Award, 5th Intl Conference, Chem. & Biol. of Mineralized Tissues
1986-90; Doctoral Excellence Fellow, Dept. of Chemistry, Rutgers University, Newark, NJ

RESEARCH SUPPORT (history & current)

Title: Evaluation of Degenerative Cartilage by Infrared Fiber Optic Probe
Funding Agency: National Medical Technology Testbed PI: Camacho
Project Dates: 6/01-12/02; 9/03 - 8/04
The major goal of this project is to develop an infrared fiber optic probe for the clinical evaluation of degeneration cartilage.

Title: Infrared Fiber Optic Imaging of Degenerative Cartilage
Funding Agency: NIH/NIBIB R01 EB00744-01 PI: Camacho
Project Dates: 9/15/02-7/30/05
The major goal of this project is to develop an infrared fiber optic probe for the clinical evaluation of degeneration cartilage.

Title: Anti-Resorptives for dysregulated bone remodeling in OI
Funding Agency: NIH/NIAMS R01 AR48337-01 PI: Camacho
Project Dates: 10/1/01-9/30/06
Overlap: None.

The major goals of this project are 1. To evaluate if an osteoclastic defect contributes to the dysregulated bone remodeling in OI. and 2. To study the effect of an anit-resorptive, OPG, on bone properties in oim/oim mice, an animal model of OI.

Title: Effect of growth hormone on articular cartilage degeneration: analysis by infrared fiber optic
Funding Agency: McCarthur Cartilage Fund, P.I: Camacho
Project Dates: 12/1/01-11/30/02
The major goal of this project is to use the the Infrared Fiber Optic Probe to evaluate the effect of growth hormone on articular cartilage degeneration.

Title: Cartilage Cell and Matrix Response to Joint Loading
Funding Agency: NIH R01 AR045748, P.I. Torzilli
Project Dates: 10/01/98 - 9/30/02
The major goal of this project is to determine how excessive joint loading effects the physical microstructure of the matrix and the function of the cells in articular cartilage.

Title: Cartilage Degeneration Following Joint Trauma
Funding Agency: NIH/NIAMS
PI/Project number: P. Torzilli, PI. R01 AR47656
Project Dates: 05/01/01-02/28/04

Title: Osteogenesis Imperfecta: Bone and Dentin Abnormalities
Funding Agency: NIH DE11803. P.I.: Camacho
Project Dates: 02/01/97 - 01/31/02
The major goal of this project is to study structural abnormalities of bone and dentin in OI

Title Application of the Infrared Fiber Optic Probe for Evaluation of Cartilage Degeneration
Funding Agency: NMTB, P.I.: Camacho
Project Dates: 6/1/01-5/31/02
This grant provides funds to develop the Infrared Fiber Optic Probe as a tool for evalnation of cartilage degeneration.

Title: Cartilage Regeneration and Repair: Analysis by Infrared Fiber Optic Probe
Funding Agency: McCarthur Cartilage Fund. P.I: Camacho
Project Dates: 9//01/98 - 10/31/00
The major goal of this project is to develop the Infrared Fiber Optic Probe as a tool for evaluation of cartilage degeneration and repair.

Funding Agency: OI Foundation, P.I.: Camacho
Title Efficacy of the bisphosphonate alendronate in increasing bone properties in infants with OI using the oim mouse model
Project Dates: 7//01/99 - 6/30/00
This grant provides funds for a Clinical Fellow to perform studies to determine the feasibility of treating infant oim/oim mouse pups (an animal model of osteogenesis imperfecta) with bisphosphonates.

Funding Agency: Children's Brittle Bone Foundation P.I.: Camacho
Title Effect of a Third Generation Bisphosphonate on Bone Properties in the Growing OIM Mouse"
Project Dates: 6//96 - 6/98
This grant provides funds to evaluate the efficacy of the bisphosphonate alendronate in treating an animal model of OI.

EXTRAMURAL PROFESSIONAL RESPONSIBILITIES

Journal Reviewer: Journa. one and Mineral Research. Calcified Tissue I. Bone. Journal of Dental Res. Connective Tissue Res

Study Sections: NIH Study Section Member SBIR Orthopaedics July 2002
Ad Hoc Reviewer NIH SBIR Orthopaedics March 2002
Ad Hoc Reviewer NSF 2001
Ad Hoc Reviewer: NIH Oral Biology Medicine 2000

Scientific Advisory Board 8th Intl Conference, Chem. & Biol. of Mineralized Tissues 2002 - current
Scientific Advisory Board 7th Intl Conference, Chem. & Biol. of Mineralized Tissues 1999 - 2001
Session Moderator: Orthopaedic Research Society Meeting 1998, 2002

Invited Lectures: Osteogenesis Imperfecta Research Advances Seminar, New York, NY October 2003
National Institute of Standards and Technology, Gaithersburg, MD October 2002
Shriner's Hospital, Montreal, Canada June 2002
Rutgers University Dept. of Mathematics, New Brunswick, NJ May 2002
National Institutes of Aging, Baltimore, MD April 2002
New Jersey Bone and Cartilage Group, New Brunswick, NJ March 2002
Osteogenesis Imperfecta Research Advances Seminar, Chicago, IL December 2001
New York Mineralized Tissue Seminar Series, NYC, NY November 2001
Orthopaedic Research Society Infrared Imaging Workshop, Orlando, FL March 2000
New Jersey OI Foundation, West Orange, NJ May 1999
American College of Rheumatology Meeting, Washington D.C. 1997

Committe Memberships:
Hospital for Special Surgery Environment of Care/Safety Committee 1998 - Current
Hospital for Special Surgery Research Safety Committee 1998 - Current
Hospital for Special Surgery Hazardous Materials and Waste Committee 1998- Current
Hospital for Special Surgery Task Force Committees - Core Facilities and Programs 2002
Hospital for Special Surgery Medical Student Education Committee 2003

Student Mentoring:
Coordinator - Bronx High School of Science Westinghouse/Intel Projects 1994 - Current
Masters Students: Angela Baechtold, University of North Carolina, Dept. of Pediatric Dentistry
Thesis Title: "Dentin Abnormalities in OIM Mice" M.S. May 2000
George Kim, City University of New York, Dept. of Biomedical Engineering
Thesis Title: "Imaging of Cartilage Degeneration" May 2003 - Current
PhD Students: Paul West, City University of New York, Dept. of Mechanical Engineering, NYC, NY
Thesis Title: "Development of an Infrared Fiber Optic Probe for Evaluation of Cartilage Degeneration" Ph.D. May 2002
Ericka Calton, City University of New York, Dept. of Biomedical Engineering,
Thesis Title "Optimization of Imaging of Degenerative Cartilage" 2002 - Current

BIBLIOGRAPHY(a. Peer reviewed articles
b. Books, reviews and chapters)

Peer Reviewed Articles:

Pleshko N, Mendelsohn R. Boskey A: A Novel IR Spectroscopic Method for the Determination of Crystallinity of Hydroxyapatite Minerals. Biophys J, 60:786. 1991.

Pleshko N, Boskey A L, Mendelsohn R: An Infrared Study of the Interaction of Polymethyl Methacrylate with the Protein and Mineral Components of Bone. J Histochem Cytochem 40:1413. 1992.

Pleshko N, Mendelsohn R, Boskey AL. An FT-IR Investigation of the Effects of Tissue Preservation on Bone. Calcif Tissue Int, 51:72, 1992.

Boskey AL, Pleshko N, Doty SB, Mendelsohn R. Applications of FT-IR Microscopy to the Study of Mineralization in Bone and Cartilage. Cells and Materials, 2:209-221, 1992.

Boskey A, Pleshko N, Mendelsohn R, Doty S, Binderman I: FT-IR Microscopic Mapping of Early Mineralization in Chick Limb-bud Mesenchymal Cell Cultures. Calcif Tissue Int, 51:443, 1992.

Camacho NP, Smith D, Goldman A, Schneider B, Young P, Berman H: Structure of an Interleukin-1 Mutant with Reduced Bioactivity Shows Multiple Subtle Changes in Conformation That Affect Protein- Protein Recognition. Biochemistry, 32:8749, 1993.

Camacho NP, Rimnac C, Meyer Jr RA, Doty SB, Boskey, AL: Effect of Abnormal Mineralization on the Mechanical Behavior of X-linked Hypophosphatemic Mice Femora. Bone 17:271-278, 1995.

Boskey AL, Camacho NP, Gadaleta S, Paschalis EP, Mendelsohn R: Applications of Fourier Transform Infrared Microscopy to the Study of Biologic Mineralization. L'Eurobiologiste 30:15-23. 1996.

Gadaleta S, Camacho NP, Mendelsohn R, Boskey AL: Fourier Transform Infrared Microscopy of Mineralized Turkey Tendon. Calcif Tissue Int, 58:17-23, 1996.

Camacho NP, Landis WJ, Boskey AL: Mineral Changes in a Mouse Model of Osteogenesis Imperfecta Detected By Fourier Transform Infrared Microscopy. Conn Tissue Res, 35:259-265, 1996.

Derfus BA, Kurtin SM, Camacho, NP, Kurup I, Ryan LM. Comparison of Matrix Vesicles Derived From Normal and Osteoarthritic Human Cartilage. Conn Tissue Res, 35: 1996.

Camacho NP, Paschalis EP, Fratzl P, Boskey AL: Analysis of Bone Ultrastructure by Fourier Transform Infrared Microscopy. J Fur Mineralstoffwechsel. 3 Jahrgang 1996. Special Edition 5/96. ISSN 1023-7763, p19-20.

Pienkowski D, Doers TM, Monier-Faugere MC, Geng Z, Camacho NP, Boskey AL, Malluche HH: Calcitonin alters bone quality in beagle dogs. J Bone Miner Res 12:1936-1943, 1997

Camacho NP, Dow D, Toledano TR, Buckmeyer JK, Gertner JM, Brayton CF, Raggio CL, Root L, Boskey AL: Identification of the oim Mutation by Dye Terminator Chemistry Combined With Automated Direct DNA Sequencing. J Orthop Res 16:38-42, 1998

Derfus B, Kranendonk S, Camacho N, Mandel N, Kushnaryov V, Lynch K, Ryan L: Human Osteoarthritic Cartilage Matrix Vesicles Generate Both Calcium Pyrophosphate Dihydrate and Apatite In Vitro. Calcif Tissue Int. 63(3): 258-262, 1998

Baechtold A , Wright JT, Yamauchi M, Spevak M, Camacho NP Dentin Composition and Structure in the oim Mouse. Proceedings of the 6th Intl Conference on the Chemistry & Biology of Mineralized Tissues, 1998

Bonewald L, Boskey A, Camacho N, Kato Y. Mineralization by Osteocyte-like Cell Lines.

Proceedings of the 6th Intl Conference on the Chemistry & Biology of Mineralized Tissues, 1998

Bostrom MPG, Camacho NP. Potential Role of Bone Morphogenetic Proteins in Fracture Healing. Clinical Orthop (supplement) 355s (October) 1998, S274-282

Hsu, H.H.T., N.P. Camacho, and Anderson, H.C. Further characterization of ATP-initiated calcification by matrix vesicles isolated from rachitic rat cartilage. Biochim. et Biophysic. Acta 1416:320-332, 1999

Hsu, H.H.T. and N.P. Camacho. Isolation of calcifiable vesicles from human atherosclerotic aortas. Atherosclerosis (in press)

Camacho NP, Hou L, Toledano TR, Ilg WA, Brayton CF, Raggio CL, Root L,Boskey AL. The Material Basis for Reduced Mechanical Properties in oim Mice Bones. J Bone Min Res 14:264-272, 1999.

Camacho NP, Rinnerthaler S, Paschalis EP, Mendelsohn R, Boskey AL, Fratzl P. Complementary information on bone ultrastructure from scanning small angle x-ray scattering and Fourier transform infrared microscopy, Bone, 1999

Blank RD, Raggio CL, Giampietro PF, Camacho NP. A genomic approach to scoliosis pathogenesis. Lupus, 8:1-5, 1999.

Camacho NP, Raggio CL, Blank RD Osteogenesis Imperfecta, Current Opinion in Orthopedics, 11:341-346, 2000

Hsu HH, Camacho NP, Sun F, Tawfik O, Aono H. Isolation of calcifiable vesicles from aortas of rabbits fed with high cholesterol diets. Atherosclerosis. 153:337-48, 2000.

Camacho NP, West P, Torzilli P, Mendelsohn R. FTIR Microscopic Imaging of Collagen and Proteoglycan in Cartilage. Biospectroscopy, 62:1-8, 2001.

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Camacho NP, Raggio CL, Doty SB, Root L, Zraick V, Ilg WA, Toledano TR, Boskey AL. A Controlled Study of the Effects of Alendronate in a Growing Mouse Model of Osteogenesis Imperfecta, Calc Tiss Int 69:94-101, 2001.

Camacho NP, West P, Griffith MH, Warren RF, Hidaka C. FT-IR imaging spectroscopy of genetically modified bovine chondrocytes. Materials Science and Engineering C 17:3-9, 2001.

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McCarthy EA, Raggio CL, Hossack MD, Miller EA, Jain S, Boskey AL, Camacho NP. Alendronate treatment for infants with osteogenesis imperfecta: demonstration of efficacy in a mouse model. Calcif Tissue Res. 52(5):660-70. 2002.

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Anderson HC, Sipe JB, Hessle L, Dhamyamraju R, Atti E, Camacho NP, Millan JL. Impaired calcification around matrix vesicles of growth plate and bone in alkaline phosphatase-deficient mice. Am J Pathol. 2004 Mar;164(3):841-7

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Garimella R, Bi X, Camacho N, Sipe JB, Anderson HC. Primary culture of rat growth plate chondrocytes: an in vitro model of growth plate histotype, matrix vesicle biogenesis and mineralization. Bone, 34(6):961-70. 2004

Book Chapters:

Gadaleta S, Paschalis E, Camacho NP, Betts F, Mendelsohn R, Boskey AL: Fourier Transform Infrared Spectroscopy of Synthetic and Biological Apatites: A Review. In: Mineral Scale Formation and Inhibition, Plennum Publishing, p 283-297, 1995.

Mendelsohn R, Boskey AL, Pleshko Camacho N: Infrared Microscopy and Imaging of Hard and Soft Tissues: Applications to Bone, Skin, and Cartilage . In: Spectrochemical Analysis Using Infrared Multichannel Detectors, Blackwell Publishing, Edited by Bhargava and Levin, 2004 in press

Description of Slides in Declaration

1. Text
2. Text
3. Schematic of Knee Joint. Articular cartilage (white in color) is present on the tibia and on the femur between the medial and lateral meniscus and the bone.
4. Schematic of Cartilage Molecular Structure. Collagen (a triple helical protein, shown as red lines) and proteoglycan (PG) are the major macromolecular components of cartilage. The collagen has zonal orientation, as reflected by directions of the red lines in the three zones of cartilage, superficial, middle, and deep zones.
5. In human osteoarthritis (OA) cartilage begins to degrade, as evidenced by fibrillation of surface cartilage, which usually indicates collagen molecular changes. A visual grading scale is used to describe this.
6. Text
7. Schematic showing emission of infrared radiation from spectrometer. Molecules vibrate at specific frequencies that are in the infrared range. As a result, an infrared spectrum can be detected and displayed on a computer. The molecular vibrations shown arise from the amide bond that occurs in proteins.
8. Schematic of incident infrared radiation (I_o) being reflected off the surface of articular cartilage (I_r). The figures displays a typical spectrum that results from sampling cartilage with an infrared fiber optic probe coupled with an attenuated total reflectance crystal.
9. The primary infrared (IR) absorptions in an IR spectrum of articular cartilage. The amide absorbances (I, II, III, and side chains) arise primarily from the amide bonds in the collagen molecule, and the proteoglycan absorbance arises primarily from the sugar groups attached to the proteoglycan molecules.
10. Schematic showing region of collagen molecule (left side) whose degradation (unraveling, breaking of molecular bonds) underlies the disease osteoarthritis. Changes in the collagen molecular structure can be detected by infrared spectroscopy. Right Side: Spectra obtained from normal (red) and degraded (black) cartilage. Subtle changes in the absorbances that arise from collagen (noted by the arrows, amide II, 1338 cm^{-1}, amide III) can be quantitated. Metrics used for spectral analysis include the ratio of the integrated area of the amide II band (at ~ 1550 cm^{-1}) and the 1338 cm^{-1} absorbance, and the ratio of the peak heights at 1238 and 1227 cm^{-1}.
11. Infrared fiber optic spectra were obtained from 12 samples of human cartilage from cartilage regions that were identified as nearly normal (grade 1) and degraded (grade 3). The ratio of the integrated area of the amide II band (at ~ 1550 cm^{-1}) and the 1338 cm^{-1} absorbance was calculated for each spectra. Means and standard deviations of the amide II/1338 cm^{-1} parameter are shown, with this ratio being higher for the degraded (grade 3) compared to the normal (grade 1) cartilage (published in West PA, Bostrom MPG, Torzilli PA, Camacho NP. FT-IR Spectral Analysis of Degenerative Cartilage: An IR Fiber Optic Probe and Imaging Study, Appl. Spectrosc., 58 [4] 376-381, 2004).
12. Text
13. Text
14. Schematic of mineralized turkey tendon. Mineral is deposited in an aligned fashion within the fibrillar collagen structure of turkey tendon. This phenomenon occurs as part

of the normal physiological state of turkeys as a mechanism to reinforce the tendon structure and make it stronger (Reference: Landis et al,)

15. Typical infrared microscopy spectrum acquired from a region of mineralization in turkey tendon. In the Gadaleta et al (1996), spatial variations in the mineral structure of the tendon were monitored by evaluation of the mineral phosphate absorbance between 900-1200 cm^{-1}.
16. Text
17. Text
18. Schematic of molecular and bulk tissues changes when an external stress is applied to a piece of articular cartilage. Bulk tissue properties can be assessed by a technique such as light scattering, and molecular properties can be assessed by a spectroscopic technique. When a piece of cartilage is stressed, i.e. compressed or stretched, the whole piece of cartilage, and thus its bulk properties, changes. Light scattering can be used to detect such a change. However, the molecular structure of the cartilage may not have changed or degraded at all during this process, and therefore the spectroscopic analysis would yield different information in comparison to the light scattering technique.